J AM COLL CARDIOL
1983;1(4):1154–9

Evaluation of a Long-Acting Converting Enzyme Inhibitor (Enalapril) for the Treatment of Chronic Congestive Heart Failure

ROBERT J. CODY, MD, FACC, ANDREW B. COVIT, MD, GARY L. SCHAER, MD, JOHN H. LARAGH, MD, FACC

New York, New York

Converting enzyme inhibition of the renin-angiotensin system has proved a valuable therapeutic approach in patients with severe chronic congestive heart failure. In the present study, a new long-acting converting enzyme inhibitor (enalapril) was evaluated with acute single dose testing (10, 20 or 40 mg) in nine patients with severe chronic congestive heart failure. Four hours after administration, there was a significant reduction of systemic vascular resistance (−19%) and pulmonary wedge pressure (−19%); in addition, there were related increases of cardiac index (+16%) and stroke index (+19%) (probability [p] ≤ 0.05 for all changes). This was associated with an increase of plasma renin activity (9 ± 3 to 35 ± 11 ng/ml per hour) and a decrease of plasma aldosterone (19 ± 4 to 9 ± 2 ng/100 ml) ($p < 0.02$ for both). With long-term therapy (1 month), there was improvement of exercise tolerance time and lessening of symptoms based on the New York Heart Association classification. Hemodynamic improvement was maintained in most, but not all, patients. There was no orthostatic hypotension during head-up tilt and hemodynamic values in the upright position were associated with normalization of intracardiac pressures. Long-term converting enzyme inhibition was indicated by a persistent increase of plasma renin activity (16 ± 2 ng/ml per hour) and a decrease of plasma aldosterone (8 ± 3 ng/100 ml). In addition, relative angiotensin II receptor occupancy was decreased as judged by the pharmacodynamic response to infusion of the angiotensin II analog saralasin.

In conclusion, the long-acting converting enzyme inhibitor, enalapril, was effective in patients with chronic congestive heart failure; however, additional studies will be necessary to further delineate the optimal dose range and identify those patients who are most likely to respond to the drug.

In severe chronic congestive heart failure, activation of the renin-angiotensin system may represent a compensatory mechanism to maintain perfusion pressure (1,2). As heart failure persists, however, angiotensin-mediated vasoconstriction and aldosterone-mediated sodium retention result in progression of the congested state. Several studies have demonstrated the short- and long-term benefits of converting enzyme inhibition in this situation (3–5). Recently, a long-acting oral converting enzyme inhibitor, enalapril (MK-421), has become available for use (6). This orally active compound is an ethyl ester converting enzyme inhibitor that undergoes deesterification to the physiologically active form (MK-422). Its theoretical advantages over captopril are a longer duration of action (7) and potential for fewer side effects because the active compound does not contain a sulfhydryl group (8). In a pilot study, we evaluated the short- and long-term hemodynamic effects of this agent in patients with severe congestive heart failure, focusing on the hemodynamic and hormonal responses. In addition, we evaluated the response to upright posture and the ability of enalapril to decrease angiotensin II receptor occupancy, as judged by the pharmacodynamic response to infusion of the angiotensin II analog saralasin.

Methods

Study patients. The study group consisted of nine patients with severe chronic congestive heart failure. All patients were normotensive, and none had experienced myocardial infarction during the previous 6 months. There were eight men and one woman ranging in age from 45 to 80 years. Six patients had ischemic and three patients had nonischemic causes for their chronic

From the Departments of Medicine and Pharmacology, New York Hospital-Cornell University Medical Center, New York, New York. This study was supported in part by General CRC Grant RR-47 from the National Institutes of Health, Bethesda, Maryland Manuscript received September 7, 1982; revised manuscript received November 16, 1982, accepted November 19, 1982.

Address for reprints: Robert J. Cody, MD, Cardiovascular Center, Section J-3, New York Hospital-Cornell University Medical Center, 525 East 68th Street, New York, New York 10021

0735-1097/83/0401154-6$03 00

J AM COLL CARDIOL
1983,1(4),1154–9

congestive heart failure. On the basis of symptoms, seven patients were in functional class IV and two patients were in functional class III congestive heart failure by the New York Heart Association classification. After giving informed consent, patients were admitted to the metabolic ward for a lead-in period of at least 4 days before hemodynamic study. Patients were maintained on a 100 mEq sodium diet; they also underwent treadmill exercise testing to fatigue, using a modified Naughton protocol. Because of the severity of their heart disease, all patients were maintained on digoxin and diuretic therapy with neither drug administered on the morning of the hemodynamic study.

Acute hemodynamic study. Hemodynamic study was performed in the morning after an overnight fast as previously described (9). Right heart catheterization was performed to measure intracardiac pressures and cardiac output by the thermodilution technique. A cannula was placed in a peripheral artery for continuous recording of systemic arterial pressure. A precordial electrocardiographic lead was used for continuous recording of the heart rate, which was expressed as beats per minute. All pressures were recorded as both phasic and electronically damped mean values. Each determination of cardiac output was measured three times and expressed as cardiac index, correcting for body surface area. Both systemic and pulmonary vascular resistance values were calculated by standard formulas (9). After placement of the catheters, a 1 hour equilibration period ensued in which baseline variables were recorded. These consisted of supine hemodynamic data and 60° head-up tilt hemodynamic data. The latter were obtained to assess orthostatic hypotension and the reflex adjustment to upright posture (5,10).

Infusion of saralasin. Significant interpatient variability of renin-angiotensin system activity may occur in chronic heart failure (11). As a rapid means to estimate this activity, administration of an angiotensin II analog such as saralasin can be used to assess relative angiotensin II receptor occupancy (12–15); that is, in patients with normal or suppressed endogenous angiotensin II receptor activity, infusion of saralasin will result in an agonist or pressor response, whereas patients with high renin-angiotensin system activity and angiotensin II receptor occupancy will demonstrate an antagonist or depressor response. Therefore, we administered saralasin as a constant infusion in standard doses (1.0 or 3.0 μg/kg per min for 15 minutes) in all of the patients during the baseline period. This infusion rate is sufficient to reveal angiotensin II receptor activity (13–15). The infusion was not only to estimate the degree of baseline renin-angiotensin system activity, but also to provide a means of estimating angiotensin II receptor activity during long-term enalapril inhibition of endogenous angiotensin II production. After all baseline determinations, a reequilibration period of 30 to 60 minutes passed, baseline measurements were again obtained and enalapril administered.

Dosage of enalapril. Clinical data regarding the optimal dose of enalapril are limited (16,17); however, in hypertensive patients, an acute reduction of blood pressure can occur with an oral dose as small as 2.5 mg. Because of these limited dose-response data, a wide range of high dose enalapril was used in this pilot study, with patients receiving 10 mg (two patients), 20 mg (five patients) or 40 mg (two patients) as a single oral dose. The hemodynamic response was monitored with recordings taken at hourly intervals for at least 4 hours after drug administration. In addition, blood samples for plasma renin activity and plasma aldosterone were obtained at 1 hour intervals after drug administration. After the acute hemodynamic response, patients were placed on long-term therapy with enalapril in a total daily dose equal to the acute dose, namely, 10 mg (four patients), 5 mg (two patients) or 2.5 mg (one patient), administered twice daily. The latter patient was given a smaller dose because of significant hypotension at higher doses. Patients were monitored clinically in the hospital for the first 3 days of drug therapy, discharged on long-term therapy and readmitted at 1 month for follow-up study.

Long-term hemodynamic study. Of the nine patients in the study group, only seven underwent long-term hemodynamic study, because one patient was lost to follow-up and another died suddenly before the 1 month study. For the long-term study, all seven patients continued on their maintenance dose of digoxin, diuretic agent and enalapril. Clinical evaluation was obtained, treadmill exercise testing performed and hemodynamic study in the supine and tilt positions performed 3 to 5 hours after the morning dose. Because long-term converting enzyme inhibition would be expected to result in marked reduction of circulating endogenous angiotensin II and angiotensin II receptor occupancy, administration of saralasin in this setting should result in an agonist or pressor response if the receptor was relatively unoccupied. Therefore, all patients received a constant infusion of saralasin at a rate identical to that of the baseline study, and the hemodynamic response was recorded. After this aspect of the study, the catheters were removed and the patients subsequently discharged.

Hormonal assay. Plasma renin activity was estimated by a radioimmunoassay technique as the generation of angiotensin I in vitro, expressed as ng/ml per hour, as previously described by our laboratory (18). Likewise, samples for plasma aldosterone were obtained and analyzed by a radioimmunoassay technique (19) and expressed as ng/100 ml.

Statistical analysis. Statistical analysis of the hemodynamic and hormonal response to short- and long-term enalapril therapy was by analysis of variance with Newman-Keuls multiple rank testing (20). Analysis of the response to tilt and saralasin infusion was by paired *t* test. All values expressed represent mean values ± 1 standard error of the mean. Changes were considered to be statistically significant at a value of $p < 0.05$.

Results

Acute Response to Enalapril

For the group, baseline hemodynamic values indicated severe chronic congestive heart failure (Table 1). This was reflected by increased pulmonary wedge pressure (21 ± 2 mm Hg), increased systemic vascular resistance (1687 ± 128 dynes/s·cm^{-5}) and decreased cardiac index (1.56 ± 0.08 liters/min per m^2) and stroke index (21 ± 3 ml/m^2). There was also pulmonary hypertension and right ventricular failure as indicated by a pulmonary artery pressure of 32 ± 2 mm Hg and right atrial pressure of 11 ± 2 mm Hg, respectively. For the group, plasma renin activity and aldosterone were also abnormally elevated at 9 ± 3 ng/ml per hour and 19 ± 4 ng/100 ml, respectively.

After oral administration of enalapril, there was a trend

Table 1. Acute Hemodynamic Response to Enalapril in Nine Patients With Chronic Heart Failure

	Baseline	1 Hour	2 Hours	3 Hours	4 Hours
HR (beats/min)	80 ± 5	81 ± 5	81 ± 6	80 ± 5	77 ± 5
$\overline{AP}$ (mm Hg)	74 ± 3	75 ± 4	72 ± 5	68 ± 4 *	67 ± 4*
$\overline{RA}$(mm Hg)	11 ± 2	12 ± 2	10 ± 2	9 ± 2	9 ± 2
$\overline{PA}$(mm Hg)	34 ± 2	36 ± 3	35 ± 2	33 ± 2	32 ± 2
$\overline{PWP}$(mm Hg)	21 ± 2	21 ± 2	18 ± 2	17 ± 2	17 ± 2*
CI (liters/min per m^2)	1.56 ± 0.08	1.69 ± 0.09	1.73 ± 0.11	1.73 ± 0.13	1.81 ± 0.13*
SI (ml/m^2)	21 ± 3	22 ± 3	22 ± 4	23 ± 3	25 ± 2*
SVR (dynes/s·cm^{-5})	1,687 ± 128	1,552 ± 110	1,520 ± 165	1,459 ± 163	1,378 ± 172*
PVR (dynes/s·cm^{-5})	362 ± 64	378 ± 48	411 ± 52	375 ± 43	354 ± 52

* Probability (p) ≤ 0.05

$\overline{AP}$ = mean arterial pressure; CI = cardiac index, HR = heart rate; $\overline{PA}$ = mean pulmonary artery pressure, PVR = pulmonary vascular resistance, $\overline{PWP}$ = mean pulmonary wedge pressure; $\overline{RA}$ = mean right arterial pressure, SI = stroke index; SVR = systemic vascular resistance

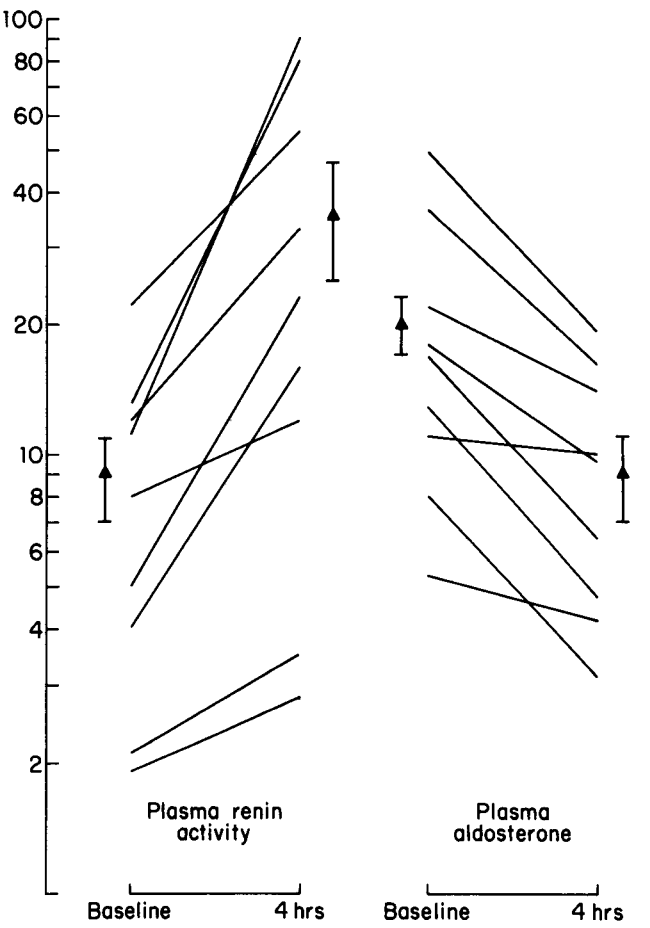
of hemodynamic improvement over the first 2 hours; however, significant hemodynamic changes were not manifest until 4 hours after drug administration. At that time, there was reduction of mean arterial pressure to 67 ± 4 mm Hg ($p < 0.02$). This was associated with a decrease in pulmonary wedge pressure to 17 ± 2 mm Hg ($p < 0.05$) and a decrease of systemic vascular resistance to 1,378 ± 172 dynes/s·cm^{-5} ($p < 0.01$) (see Table 1). The reduction of systemic resistance was associated with an increase in cardiac index to 1.81 ± 0.13 liters/min per m^2 ($p < 0.02$) and stroke index to 25 ± 2 ml/per m^2 ($p < 0.01$). Evidence of converting enzyme inhibition was revealed by the reflex increase of plasma renin activity to 35 ± 11 ng/ml per hour and decrease of plasma aldosterone to 9 ± 2 ng/100 ml, both $p < 0.02$ (Fig. 1). Baseline plasma renin activity was correlated with the percent decrease of systemic vascular resistance ($r = 0.670$) and percent increase of cardiac index ($r = 0.684$) at 4 hours after enalapril administration ($p < 0.05$ for both). Hemodynamic measurements were also obtained at 6 and 8 hours in several patients in whom evidence of hemodynamic improvement persisted. In five patients, repeat hemodynamic measurements were made at 24 hours, at which time there was no evidence of residual hemodynamic changes.

Long-term Response to Enalapril

For the seven patients maintained on enalapril therapy for 1 month, there was improvement in exercise tolerance time and functional class (Fig. 2). Exercise time increased from 122 ± 61 to 344 ± 90 seconds ($p < 0.02$). Functional class improved by two classes in two patients and by one class in four patients; it was unchanged in one patient.

The hemodynamic improvement at 1 month for the group and for individual patients is shown in Table 2. Compared with the control phase, there was a significant reduction in mean arterial pressure (65 ± 1 mm Hg) and reduction of systemic vascular resistance (1,317 ± 60 dynes/s·cm^{-5}). The reduction in systemic resistance was associated with a significant increase in cardiac index to 1.81 ± 0.08 liters/min per m^2 and stroke index that increased to 24 ± 1 ml per m^2. In most patients, there was long-term reduction in pulmonary wedge pressure; however, this reduction did not achieve statistical significance for the group because Patient

Figure 1. Acute converting enzyme inhibition and blockade of the renin-angiotensin system after short-term administration of enalapril. Both the increase in plasma renin activity (ng/ml per hour) and decrease in plasma aldosterone (ng/100 ml) were significant ($p < 0.02$).



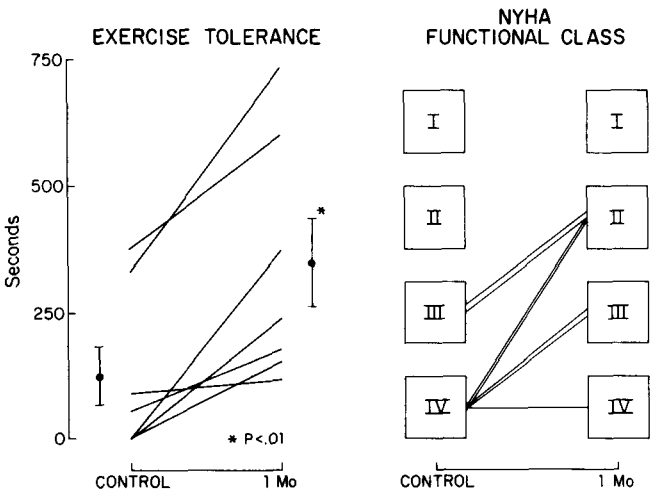


Figure 2. Improvement of exercise tolerance time ($p < 0.02$) and New York Heart Association (NYHA) functional classification after 1 month of enalapril therapy

3 had an increase of pulmonary wedge pressure at 1 month of enalapril therapy compared with the control phase. Overall, there was no significant change in heart rate, right atrial and pulmonary artery pressures or pulmonary vascular resistance at 1 month. Evidence for chronic converting enzyme inhibition for the group was a persistent increase in plasma renin activity to 16 ± 2 ng/ml per hour ($p < 0.05$) and reduction in plasma aldosterone to 8 ± 3 ng/100 ml ($p < 0.05$) compared with control.

The hemodynamic response to upright posture was also evaluated at 1 month of enalapril therapy (Table 3). No orthostatic hypotension was observed despite significant reduction in cardiac filling pressures during head-up tilt. In addition to supine hemodynamic improvement, the upright hemodynamic data during long-term enalapril therapy were better than both supine and tilt hemodynamic data during the control phase.

Effects of saralasin infusion. To determine the extent of angiotensin II receptor vacancy due to reduction of circulating angiotensin II by enalapril, saralasin was infused (Fig. 3). The response during the control phase was heterogeneous because of interpatient variability of renin-angiotensin system activity and, therefore, angiotensin II receptor activity. After 1 month of enalapril therapy, however, when endogenous angiotensin II generation was blocked at the converting enzyme, the response to saralasin was uniformly agonistic: there was a 20% increase in systemic vascular resistance ($p < 0.01$), resulting in a 10% increase in arterial pressure ($p < 0.05$). Because of the increased systemic resistance, there was an increase in pulmonary capillary wedge pressure ($+30\%$, $p < 0.001$) and a decrease in cardiac index (-25%, $p < 0.001$). This agonist response to saralasin during enalapril therapy provided further evidence that endogenous angiotensin II generation was inhibited.

Table 2. Long-term Response to Enalapril in Seven Patients With Chronic Heart Failure

Patient	HR	$\overline{AP}$	$\overline{RA}$	$\overline{PA}$	$\overline{PWP}$	CI	SI	SVR	PVR
					Control				
1	85	84	9	40	18	1.33	16	2,400	704
2	93	80	18	36	25	1.30	14	2,112	352
3	64	80	13	25	17	1.60	25	1,536	176
4	104	72	18	46	32	1.20	12	1,720	440
5	58	61	4	36	26	1.85	32	1,208	208
6	80	66	6	24	12	1.91	24	1,224	240
7	77	62	10	28	20	1.60	21	1,511	237
Mean	80	72	11	34	22	1.54	20	1,673	337
SEM	±6	±4	±2	±3	±3	± 0.10	±3	±168	±70
					1 Month				
1	77	68	1	29	15	2.09	27	1,384	288
2	85	64	10	40	18	1.91	23	1,216	488
3	60	67	12	34	25	1.44	24	1,376	224
4	93	70	11	40	24	1.75	19	1,296	344
5	61	60	7	28	14	1.75	29	1,184	304
6	92	62	6	20	11	1.95	21	1,151	248
7	70	64	4	27	14	1.81	26	1,610	349
Mean	77	65	7	31	17	1.81	24	1,317	321
SEM	±5	±1	±2	±3	±2	±0.08	±1	±60	±33
p*	NS	0.05	NS	NS	NS	0.05	0.05	0.05	NS

*Significance at 1 month versus control
NS = not significant, p = probability, SEM = standard error of the mean; other abbreviations and units as in Table 1

Table 3. Effect of Long-term Enalapril on Postural Hemodynamics

	Control		1 Month	
	Supine	Tilt	Supine	Tilt
HR	81 ± 6	85 ± 5	77 ± 5	82 ± 5
$\overline{AP}$	72 ± 3	65 ± 1	65 ± 1	63 ± 4
$\overline{RA}$	11 ± 2 *	4 ± 2	7 ± 2 *	3 ± 2
$\overline{PA}$	35 ± 3 *	23 ± 5	31 ± 3 *	24 ± 4
$\overline{PWP}$	20 ± 3 *	11 ± 4	17 ± 2 *.	12 ± 3
CI	1.60 ± 0.14	1.49 ± 0.10	1.81 ± 0.08	1.66 ± 0.07
SI	21 ± 3	19 ± 2	24 ± 1	22 ± 2
SVR	1,643 ± 203	1,704 ± 183	1,317 ± 60	1,476 ± 90

* Asterisks indicate a significance level of at least $p < 0.05$.
Abbreviations and units as in Table 1.

Discussion

Side effects and dosage. Long-term use of enalapril was associated with subjective and objective improvement in most of our patients. There were no major side effects during this period of observation, and one of the seven patients with asymptomatic hypotension required downward adjustment of his enalapril dosage. The death of one patient that occurred during the period of observation was a sudden death in a person with documented high grade ventricular ectopic rhythm. Effective daily dosage ranged from 2.5 to 10 mg, administered twice daily. The range of dosage was associated with hemodynamic improvement and hormonal evidence of complete converting enzyme inhibition, and was similar to the dosage used thus far in patients with hypertension (16,17).

Acute effects. During the short-term study, significant hemodynamic changes were observed at 4 hours. Therefore, this may represent the peak effect or the peak effect may actually occur somewhat after this period of time (7,17). Unlike captopril, whose peak hemodynamic and hormonal effect occurs 1 to 1.5 hours after administration (21), the effect of enalapril would be expected to peak later because the drug is administered in a prodrug form and has to undergo deesterification to the active compound (6,7).

Long-term effects. Enalapril was continued on a long-term basis with digoxin and diuretic therapy, and most patients demonstrated lessening of symptoms and increased exercise tolerance. In most patients, there was a reduction of systemic vascular resistance and an increase of cardiac index; however, this was not uniform. For the group, the response to upright tilt was notable for absence of orthostatic hypotension, improvement of supine and upright hemodynamic status compared with the control state and, particularly, normalization of cardiac filling pressures in the upright position. Persistent converting enzyme inhibition was indicated by increased plasma renin activity, decreased plasma aldosterone and reduced angiotensin II receptor occupancy as judged by pharmacologic stimulation of the receptor. After the 1 month study, five patients were maintained on enalapril therapy, prazosin was added to enalapril in a sixth patient and enalapril was discontinued in a seventh patient because of poor response.

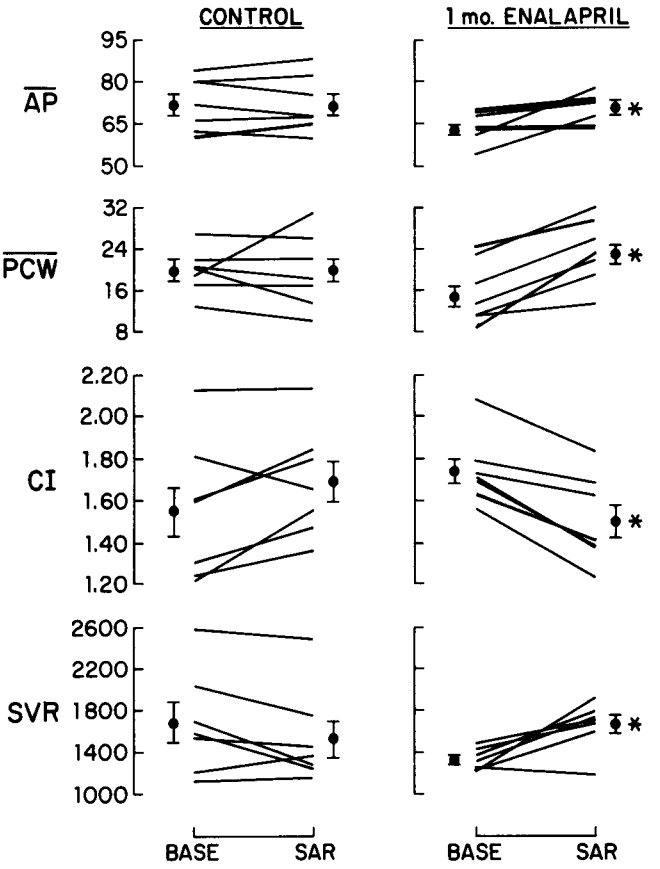


Figure 3. The agonist/antagonist saralasin (SAR) was used to assess angiotensin II receptor occupancy in patients with heart failure who subsequently received long-term therapy with enalapril. In the baseline state **(left)**, there were varied hemodynamic responses to saralasin due to the interpatient range of plasma renin activity. With 1 month of enalapril therapy **(right)**, a uniform agonist or pressor response was observed in all patients, indicating significant reduction of endogenous angiotensin II generation. **Asterisks** indicate significant hemodynamic changes. $\overline{AP}$ = mean arterial pressure (mm Hg); CI = cardiac index (liters/min per m^2); $\overline{PCW}$ = mean pulmonary capillary wedge pressure (mm Hg); SVR = systemic vascular resistance (dynes/s·cm^{-5}).

Therapeutic implications. This study represents a pilot study of this new long-acting converting enzyme inhibitor in patients with chronic heart failure. Several points are noted as a result of these initial data. First, the delayed onset of enalapril action and its prolonged effect obscure the peak response and duration of action, so that continuous hemodynamic and hormonal monitoring for at least 12 hours would be required. This is difficult not only in terms of patient tolerance, but also because of changes in baseline hemodynamic values and diurnal variation in renin release (22). Second, the optimal dose of enalapril is not clear,

although animal studies (7) demonstrate that relatively small doses are sufficient to block the pressor effect of exogenously administered angiotensin I. From the present study, it would appear that a dose of 10 or 20 mg administered for a short period of time, and 5 or 10 mg administered twice daily should be sufficient to inhibit the angiotensin-converting enzyme in most patients. This conclusion is drawn from the evidence of blockade of aldosterone production and reduction of angiotensin II receptor occupancy as judged by pharmacologic stimulation of the receptor.

These points will require additional studies for clarification. Furthermore, because the peak response to enalapril is difficult to identify in this short-term study, it was difficult to correlate the extent of hemodynamic improvement with baseline plasma renin activity as has been done in previous studies of converting enzyme inhibitors (8). It has become evident that interruption of angiotensin II-mediated vasoconstriction and aldosterone-mediated sodium retention is an important facet of the therapeutic approach to severe chronic congestive heart failure. Therefore, continued studies of enalapril regarding both its pharmacodynamic and physiologic effects seem warranted.

We gratefully acknowledge the clinical and technical expertise of Kathleen Pondolfino, RN, in the performance of this study. We are indebted to Merck, Sharp & Dohme, especially Drs. Davies and Mantell, for their support.

References

1. Laragh JH. Hormones in the pathogenesis of congestive heart failure: vasopressin, aldosterone, and angiotensin II. Circulation 1962;25:1015–23.
2. Chonko AM, Bay WH, Stein JH, Ferris TF. The role of renin and aldosterone in the salt retention of edema. Am J Med 1977;63:881–9.
3. Ader R, Chatterjee K, Ports T, et al. Immediate and sustained hemodynamic and clinical improvement in chronic heart failure by an oral angiotensin-converting enzyme inhibitor. Circulation 1980;61:931–7.
4. Levine TB, Franciosa JA, Cohn JN. Acute and long-term response to an oral converting enzyme inhibitor, captopril, in congestive heart failure. Circulation 1980;62:35–41.
5. Cody RJ, Franklin KW, Kluger J, Laragh JH. Mechanisms governing the postural response, and baroreceptor abnormalities in chronic congestive heart failure: effects of acute and long-term converting enzyme inhibition. Circulation 1982;66:135–43.
6. Patchett AA, Harris E, Tristam EW, et al. A new class of angiotensin converting enzyme inhibitors. Nature 1980;288:280–3.
7. Gross DM, Sweet CS, Ulm EH, et al. Antihypertensive activity of N-/(S)-1-carboxy-3-phenylpropyl/-L-Ala-L-Pro and its ethyl ester (MK-421) on angiotensin converting enzyme in vitro and angiotensin I pressor responses in vivo. J Pharmacol Exp Ther 1981;216:552–7.
8. Vlasses PH, Ferguson RK, Chatterjee K. Captopril: clinical pharmacology and benefit-to-risk ratio in hypertension and congestive heart failure. Pharmacotherapy 1981;2:1–16.
9. Kluger J, Cody RJ, Laragh JH. The contributions of sympathetic tone and the renin-angiotensin system to severe chronic congestive heart failure. response to specific inhibitors. Am J Cardiol 1982;49:1667–74.
10. Cody RJ. The effect of captopril on postural hemodynamics and autonomic responses in chronic heart failure. Am Heart J 1982;104:1190–5.
11. Cody RJ, Laragh JH. Use of captopril to estimate renin-angiotensin-aldosterone activity in the pathophysiology of chronic heart failure. Am Heart J 1982;104:1184–9.
12. Turini GA, Brunner HR, Ferguson RK, Rivier JL, Garvas H. Congestive heart failure in normotensive man: haemodynamics, renin, and angiotensin II blockade. Br Heart J 1978;40:1134–42.
13. Wallace JM, Case DB, Laragh JH, Keim HJ, Drayer JH, Sealey JE. The immediate pressor response to saralasin in man: a test of angiotensin II receptor vacancy. Circ Res 1979;44:38–45.
14. Cody RJ, Fouad FM, Tarazi RC, Bravo EL. Hemodynamic effects of a new angiotensin-antagonist (Sar^1Thr^8) angiotensin II in hypertensive man. Circulation 1980;61:338–44.
15 Cody RJ, Schaer G, Covit A, Laragh JH. Identification of angiotensin II receptor occupancy in chronic heart failure with saralasin infusion (abstr). Clin Res 1982;30:178A.
16. Gavras H, Biollaz J, Waeber B, Brunner HR, Bavras I, Davies RO. Antihypertensive effect of the new oral angiotensin converting enzyme inhibitor "MK-421". Lancet 1981;2:543–7.
17. Ferguson RK, Vlasses PH, Swanson BN, et al. Effects of enalapril, a new converting enzyme inhibitor, in hypertension. Clin Pharmacol Ther 1982;32:48–53.
18. Sealey JE, Laragh JH. How to do a plasma renin assay. Cardiovasc Med 1977;2.1079–92.
19 Sealey JE, Buhler FR, Laragh JH, Manning EL, Brunner HR. Aldosterone excretion: physiologic variations in man measured by radioimmunoassay or double-isotope dilution Circ Res 1972;31:376–87.
20 Zar JH. Biostatistical Analysis. Englewood Cliffs, NJ: Prentice Hall, 1974;151–5.
21. Cody RJ, Schaer GL, Covit AB, Pandolfino K, Williams G. Captopril kinetics in chronic congestive heart failure. Clin Pharmacol Ther 1982;32:721–6.
22. Williams GH, Cain JP, Dluhy RG, Underwood RH. Studies of the control of plasma aldosterone concentration in normal men. J Clin Invest 1972;51:1731–42.